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Reduced Left Subgenual Anterior Cingulate Cortical Activity during Withdrawal-related Emotions in Melancholic Depressed Female Patients

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Abstract

Background: Research regarding the neurocircuitry in mood disorders suggests an important role for affective information processing of the subgenual part of the anterior cingulate cortex (Cg25: Brodmann area 25).

Objective: In this study, we focused on Cg25 neuronal responses in depressed females using a paradigm in which emotions are elicited without explicit cognitive control, relying on the salient nature of the mood inducing stimuli eliciting approach-related emotions (like happiness) or withdrawal-related emotions (like disgust).

Methods: Twelve treatment-resistant melancholic depressed women and 12 healthy female control subjects were asked to passively view blocks of emotionally valenced baby faces while undergoing functional magnetic resonance imaging (fMRI).

Results: Compared to the healthy females, the depressed patients displayed significantly higher bilateral Cg25 neuronal activities in both emotional conditions. In melancholically depressed women, we found significantly less left-sided than right-sided Cg25 neuronal activity during the withdrawal-related emotions, while right-sided Cg25 activity was comparable for both emotional responses.

Conclusions: Our results indicate that in depressed women the left Cg25 modulates intense visceral emotional responses to aversive visual stimuli. This could help explain why the left Cg25 provides a valid target region for antidepressant treatment strategies in unipolar melancholic depression.

Keywords: Melancholic depression, Subgenual cingulate cortex, Emotion

1. Introduction

In depressed patients, the subgenual prefrontal cortex (Cg25: Brodmann area 25) has consistently been shown to be metabolically hyperactive (Drevets et al., 1997; Greicius et al., 2007). Non-pharmacological strategies for the treatment of refractory depression, such as deep brain stimulation (DBS) and anterior cingulotomy, specifically target the Cg25 (Mayberg et al., 2005; Johansen-Berg et al., 2008; Dougherty et al., 2003; Steele et al., 2008). In addition, clinical efficacy of nervus vagus stimulation (VNS) therapy seems to correlate with decreases in left Cg25 activity (Zobel et al., 2005). Animal models suggest that the right Cg25 facilitates the expression of visceral responses during emotional processing and that the left modulates these responses (Sullivan and Gratton, 1999, Drevets, 2000).

Although the Cg25 is an important target area in the treatment of affective disorders, its involvement in the evaluation of emotional salience of visual stimuli during depressed episodes is not quite understood (Öngür et al. 1998; Surgeladze et al., 2005). By using happy and sad looking adult faces, Gotlib and co-workers (2005) demonstrated increased Cg25 activation in male and female depressed patients compared to healthy controls. Because gender can influence brain imaging outcome results (Wager et al., 2003) and because Cg25 dysfunctions seem to be predominantly present in melancholically depressed patients (Pizzagalli et al., 2004), we focused especially on medication-free female depressed patients of the melancholic subtype. We used positively and negatively valenced baby faces as mood inducing stimuli, respectively eliciting approach-related and withdrawal-related emotions (Baeken et al., in press).

Studies indicate that infant faces elicit stronger emotional responses in viewers than those of adults (Best et al., 1994). From an 'evolutionary' perspective, we anticipated that baby faces would strongly engage attention and would induce spontaneous emotional reactions in female subjects (Bradley et al., 2003; Compton, 2003).

We hypothesized that compared to healthy controls depressed female patients would display significantly higher bilateral Cg25 neuronal activities in both emotional responses. In depressed women, we expected significant differences between approach and withdrawal emotional conditions in the left Cg25 neuronal activity because of the modulating function of this brain region.

2. Materials and Methods

2.1. Stimuli

Baby face pictures from both genders were used (mean estimated age=5.5 months, SD=4.0). All babies were looking directly at the camera. Neutral pictures, matched for colour and luminosity, were obtained on the basis of a set of baby face pictures by reduction of the image matrix and by smoothing the resulting pictures using CorelDRAW 11 (See Fig. 1). Earlier research had already demonstrated that passively viewing these positively valenced baby faces evoked approach-related emotions in females, and viewing the negatively valenced baby faces evoked withdrawal-related emotions (Baeken et al., in press).

2.2. Imaging Study

2.2.1. Subjects

The Institutional Review Board of our University Hospital approved the study and all subjects gave written informed consent. Two groups of twelve right-handed female subjects each were recruited for the fMRI study (depressed patients: mean age=36.0years, SD=10.9; volunteers: mean age=30.2years, SD=8.1). An independent T-test showed no significant age difference between the two groups (T(22)=1.36,p=0.19). Three volunteers and five patients were mothers.

Subjects taking medication, other than birth-control pills, were excluded. After a washout period of their antidepressants (AD) all patients were AD free for at least two weeks. Psychiatric disorders were assessed by the Dutch version of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). All unipolar depressed patients were of the melancholic subtype and were at least stage II treatment resistant as described by Rush et al. (2003). Severity of depression was assessed by the 21-item Beck Depression Inventory (BDI, Beck et al., 1984). Mean BDI scores were 28.0,SD=9.7, indicating severe depression. Female volunteers with a psychiatric disorder or a score higher than eight on the BDI were excluded.

2.2.2. fMRI design

During fMRI scanning, stimuli followed a blocked design with 13 blocks of 36 seconds (or 10 pictures) each. To control for carryover effects between conditions, the blocks were organized in a counterbalanced fashion. Images were displayed for 3.6 seconds and preceded by a short flash of a black crosshair centred on a white background,

introduced for fixation purposes. All subjects were given no instructions other than to watch the pictures attentively and each stimulus image was shown only once.

2.2.3. Image acquisition and data analysis

The study was carried out on a 1.5T MRI scanner (Philips Intera, Best, The Netherlands). We measured 156 consecutive FFE-EPI volumes (TR/TE=3000/35msec, flip angle=90°, 18 slices, slice thickness/gap=5.0/1.0mm, size=64x64, in plane resolution=3.75x3.75 mm, duration 7min 48sec) covering the whole brain. The fMRI data were analyzed with SPM5 software (Wellcome Department of Cognitive Neurology, London, UK). The fMRI time series were realigned to their first volume to correct for head movements, normalized into the standard anatomical space (EPI MNI template) and smoothed with an 8 mm Gaussian kernel.

For each subject, we estimated condition effects using the general linear model (Friston et al., 2003). We modeled the 3 regressors of interest, positive, negative and neutral, as separate boxcar functions convolved with the canonical hemodynamic response function. For each subject, we generated contrast (percentage signal change) maps and T-statistic maps corresponding to the contrasts positive versus neutral and negative versus neutral. Starting from the individual contrast maps, we performed a 1-sample T-test for each contrast and for each group. The T-statistic maps of this random effects analysis were thresholded with p (uncorrected)<0.001.

To provide statistical evidence of lateralized Cg25 emotional functioning, a region of interest (ROI) based analysis was performed in Marsbar (Brett et al., 2002). By using the WFU PickAtlas Tool Version, 2.4 (Maldjian et al., 2003), we defined mask-volumes which masked all brain activations except those in the left or right Cg25

containing both activated and non-activated voxels in proportions depending on the general activity level of each individual. To take this inter-subject variability into account, we adjusted the threshold for the activation pixels for each subject using a technique that was introduced earlier by a number of other authors in order to improve the robustness of lateralization measures (Fernández et al., 2001; Knecht et al., 2003; Jansen et al., 2006). In a first step, we calculated the means of the 5% highest T-values in the left and right Cg25 regions as defined by the mask. In a second step, voxels with a T-value above 20% of this mean T were selected. Signal versus time curves were extracted by averaging the signal of all voxels in the two ROI's for each dynamic. This resulted in individual percentage of signal change values for both contrasts in the left and right Cg25 and were further used in SPSS 15 (SPSS, Chicago, IL).

To provide statistical evidence of lateralized functioning of Cg25 in relation to approach and withdrawal-related emotions, we started from the individual contrast values and we performed a mixed three-way ANOVA analysis (2x2x2 design) with lateralization (left vs. right Cg25) and emotion (approach vs. withdrawal) as within-subject factors and group (healthy control vs. patient) as between-subjects factor. Two-way ANOVA's, paired and independent T-tests completed the analysis. Significance threshold for all SPSS analyses was set at a two-tailed probability of $p \leq 0.05$.

3. Results

The results are summarized in Fig 2.

By looking at the results of the three-way ANOVA analysis for Cg25, we found a significant main effect of group ($F(1,22)=14.33, p<0.01$), but no main effects of emotion ($F(1,22)=0.49$, $p=0.49$), nor lateralization ($F(1,22)=1.99, p=0.17$). No significant interaction effects between group and emotion ($F(1,22)=0.30, p=0.59$), between group and lateralization ($F(1,22)=2.52, p=0.13$) and between emotion and lateralization ($F(1,22)=2.32, p=0.14$) were observed. However, the three-way interaction between emotion, lateralization and group reached significance ($F(1,22)=4.80, p=0.04$). Two-way ANOVA's for each group separately only reached significance for the interaction effect between emotion and lateralization in TRD patients ($F(1,11)=5.77, p=0.04$).

Independent T-tests, to investigate group differences, showed that for the approach-related emotional experiences, left Cg25 activity was significantly higher for depressed patients (mean=0.38,SD=0.22) compared to the control group (mean=0.08,SD=0.11) ($T(22)=4.17, p<0.01$). The same pattern was found for right Cg25 activity (mean patients=0.36,SD=0.28; mean controls=0.09,SD=0.11:$T(22)=3.14, p<0.01$). Independent T-tests revealed that the withdrawal-related emotional experiences yielded comparable results for the left Cg25 (mean patients=0.28,SD=0.21; mean controls=0.09,SD=0.11:$T(22)=2.89, p<0.01$) and for the right Cg25 (mean patients=0.39,SD=0.25; mean controls=0.07,SD=0.18:$T(22)=4.08, p<0.01$).

To further explore intra-individual differences in the TRD group, paired T-tests were used. A significant difference in left-right Cg25 activity was present for processing

withdrawal-related emotions (T(11)=3.61,p=0.01), showing more activity in the right Cg25 (mean=0.39,SD=0.25), compared to the left Cg25 (mean=0.28,SD=0.21). Approach-related emotions showed no Cg25 lateralization (p>0.05). Left Cg25 activity was significantly lower in the processing of withdrawal-related emotions (mean=0.28,SD=0.21), compared to approach-related emotions (mean=0.38,SD=0.22) (T(11)=2.29,p=0.04). The right Cg25 showed no differentiated involvement in the processing of both emotional conditions (p>0.05).

4. Discussion

In line with other 'passive viewing' functional brain imaging studies using visual emotional paradigms (Mourão-Miranda et al., 2003), we found predominantly bilateral posterior brain activity while the subjects were processing both blocks of baby faces. See Fig1. The occipital, fusiform and posterior temporal visual cortices involved play a critical role in the perceptual processing of socially and emotionally relevant visual stimuli (Lang et al., 1998; Adolphs, 1999).

As hypothesized and in line with the results of Gotlib et al (2005), we found that in depressed women both approach- and withdrawal-related emotions resulted in higher bilateral Cg25 activity, indicating stronger autonomic emotional responses compared to controls. A possible explanation for the elevated neural responses to positively valenced baby faces could be that depressed patients respond to pleasant stimuli as though they were signals of frustrative non-reward (Allen et al., 1999). Further, Rottenberg (2002)

demonstrated that autonomic physiological responses, such as heart rate reactivity, were highest when depressed patients were engaged in pleasurable film clips.

Whereas in the depressed group approach-related emotions evoked comparable activation patterns in both left and right Cg25, withdrawal-related emotions only activated the right Cg25 on the same level, confirming its facilitating status to visceral responses during emotional processing in general. During withdrawal-related emotions, the left Cg25 was less strongly activated, as our analysis showed a significantly lower degree of activation compared to the processing of positively valenced baby faces. During withdrawal-related emotions, left Cg25 activity was also significantly lower compared to its right counterpart. As depressed patients have more difficulties to disengage from negative emotional stimuli (Goeleven et al., 2006; Leyman et al., 2007), inhibitory control of sustained left Cg25 responses, resulting in diminished neuronal activity, might be of essence for adaptive and unsustained emotional responses (Matthews et al., 2009). Although at this point speculative, these observations could indicate that in depressed women the left Cg25 modulates intense visceral emotional responses to aversive visual stimuli by limiting their neuronal impact. This corresponds to earlier reports of decreased left sided limbic activation patterns in response to negative stimuli in majorly depressed patients (Davidson et al., 2003; Lee et al., 2007). Additionally, voluntary suppression of negative affect was found to activate prefrontal cortical areas accompanied by attenuation in brain activity within limbic regions (Phan et al., 2005). Importantly, this lower degree of left Cg25 activity in the withdrawal-related emotional condition was still significantly higher compared to healthy females.

Limitations

As the sample was relatively small, our results should be interpreted cautiously. Due to the nature of this study, we can only draw conclusions regarding right-handed melancholically depressed women. The fact that emotional valence and arousal may be controlled by different neural systems - the negative and neutral baby faces are not equal in arousal levels - (Garavan et al., 2001; Gerber et al., 2008) and that some of the participants were mothers, might have introduced extra variability in our data. That all our subjects were AD-free when scanned can be considered as a major advantage of the study (Kumari et al., 2003; Serra et al., 2006).

Conclusions

Compared to non-depressed female subjects, melancholically depressed patients displayed higher bilateral Cg25 activities in both approach- and withdrawal-related emotional responses, indicating stronger autonomic emotional responses in depressed women. Our results support former findings of abnormal left Cg25 neuronal activity during major depression and our data could add some further explanation as to why the Cg25 forms a valid target region in the treatment of affective disorders.

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References

Adolphs, R., 2002. Neural systems for recognizing emotion, Curr Opin Neurobiol. 12, 169-177.

Allen, B.A., Trinder, J., Brennan, C., 1999. Startle modulation in clinical depression: Preliminary findings. Biol Psychiatry.4,542–550.

Baeken, C., Van Schuerbeek, P., De Raedt, R., Bossuyt, A., Vanderhasselt, M.A,. De Mey, J. , Luypaert, R., in press. Passively viewing negatively valenced baby faces attenuates left amygdala activity in healthy females scoring high on 'Harm Avoidance'. Neuroscience Letters.

Beck, A.T .& Steer, R.A.., 1984. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol. 40, 1365-1367.

Best, C.T., Womer, J.S., Queen, H.F.., 1994.Hemispheric asymmetries in adults' perception of infant emotional expressions. J Exp Psychol Hum Percept Perform. 20,751-765.

Bradley, MM, Sabatinelli, D, Lang, PJ, Fitzsimmons, JR, King, W, Desai, P., 2003Activation of the visual cortex in motivated attention. Behav Neurosci.117, 369-380.

Brett, M., Anton, J.L., Valabregue, R., 2002. Region of interest analysis using an SPM toolbox [abstract]. Presented at the Eighth International Conference of Functional Mapping of the Human Brain, June 2–6, 2002, Sendai, Japan. Available on CD-ROM in NeuroImage, Vol. 16, No. 2.

Compton, R.J., 2003. The interface between emotion and attention: a review of evidence from psychology and neuroscience. Behav Cogn Neurosci Rev.2, 115-129.

Davidson, R.J., Irwin, W., Anderle, M.J., Kalin, N.H., 2003. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry.160,64-75.

Dougherty, D.D., Weiss, A.P., Cosgrove, G.R., Alpert, N.M., Cassem, E.H., Nierenberg, A.A., Price, B.H., Mayberg, H.S., Fischman, A.J., Rauch, S.L., 2003. Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. J Neurosurg.99,1010-1017.

Drevets, W.C., Price, J.L., Simpson, J.R., Todd R.D., Reich, T., Vannier, M., Raichle, .M.E., 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature.386,824-827.

Drevets, W.C., 2000. Neuroimaging studies of mood disorders. Biol Psychiatry.48:813-29.

Fernández, G., de Greiff, A., von Oertzen, J., Reuber, M., Lun, S., Klaver, P., Ruhlmann, J., Reul, J., Elger, C.E., 2001. Language mapping in less than 15 minutes: real-time functional MRI during routine clinical investigation. NeuroImage. 14, 585–594.

Friston, K.J., Harrison, L., Penny, W., 2003. Dynamic causal modelling. Neuroimage.19, 1273-1302.

Garavan, H., Pendergrass, J.C., Ross, T.J., Stein, E.A., Risinger, R.C., 2001. Amygdala response to both positively and negatively valenced stimuli. Neuroreport. 12, 2779-2783.

Gerber, A.J., Posner, J., Gorman, D., Colibazzi, T., Yu, S., Wang, Z., Kangarlu, A., Zhu, H., Russell, J., Peterson, B.S., 2008. An affective circumplex model of neural

systems subserving valence, arousal, and cognitive overlay during the appraisal of emotional faces. Neuropsychologia.46,2129-2139.

Goeleven, E., De Raedt, R,. Baert, S., Koster, E.H.., 2006. Deficient inhibition of emotional information in depression. J Affect Disord. 93,149-157.

Gotlib, I.H., Sivers, H., Gabrieli, J.D., Hallmayer, J., 2005. Subgenual anterior cingulate activation to valenced emotional stimuli in major depression. Neuroreport.16,1731-1734.

Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., Reiss, A.L., Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol Psychiatry.62,429-437.

Jansen, A., Menke, R., Sommer, J., Förster, A.F., Bruchmann, S., Hempleman, J., Weber, B., Knecht, S., 2006. The assessment of hemispheric lateralization in functional MRI--robustness and reproducibility. Neuroimage.33,204-217.

Johansen-Berg, H., Gutman, D.A., Behrens, T.E., Matthews, P.M., Rushworth, M.F., Katz, E., Lozano, A.M., Mayberg, H.S., 2008. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. J Nerv Ment Dis.196,405-410.

Knecht, S, Jansen, A, Frank, A, van Randenborgh, J, Sommer, J, Kanowski, M, Heinze, HJ., 2003 How atypical is atypical language dominance? Neuroimage.18,917-927.

Kumari, V., Mitterschiffthaler, M.T., Teasdale, J.D., Malhi, G.S., Brown, R.G., Giampietro, V., Brammer, M.J., Poon, L., Simmons, A., Williams, S.C., Checkley,

S.A., Sharma, T., 2003. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. Biol Psychiatry. 54,777-791.

Lang, P.J., Bradley, M.M., Fitzsimmons, J.R., Cuthbert, B.N., Scott, J.D., Moulder, B., Nangia, V., 1998. Emotional arousal and activation of the visual cortex: an fMRI analysis, Psychophysiology. 35, 199-210.

Lee, B.T,. Seong Whi Cho , Hyung Soo Khang , Lee, B.C., Choi, I.G., Lyoo, I.K., Ham, B.J., 2007. The neural substrates of affective processing toward positive and negative affective pictures in patients with major depressive disorder. Prog Neuropsychopharmacol Biol Psychiatry.31,1487-1492.

Leyman, L., De Raedt, R., Schacht, R., Koster, E.H., 2007. Attentional biases for angry faces in unipolar depression. Psychol Med. 37,393-402.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fmri data sets. NeuroImage.19, 1233– 1239.

Matthews, S., Simmons, A., Strigo, I., Gianaros, P., Yang, T., Paulus, M., 2009. Inhibition-related activity in subgenual cingulate is associated with symptom severity in major depression. Psychiatry Res.172, 1-6.

Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwalb, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. Neuron.45,651-660.

Mourão-Miranda, J., Volchan, E., Moll, J., de Oliveira-Souza, R., Oliveira, L., Bramati, I., Gattass, R., Pessoa, L., 2003. Contributions of stimulus valence and arousal to visual activation during emotional perception, Neuroimage. 20, 1955-1963.

Ongur, D., Drevets, W.C., Price, J.L., 1998. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A. 95,13290-13295

Phan, K.L., Liberzon, I., Welsh, R.C., Britton, J.C., Taylor, S.F., 2003. Habituation of rostral anterior cingulate cortex to repeated emotionally salient pictures. Neuropsychopharmacology. 28, 1344-1350.

Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J. , 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. Mol Psychiatry. 9: 325.

Rottenberg, J., Kasch, K.L., Gross, J.J., Gotlib, I.H., 2002. Sadness and amusement reactivity differentially predict concurrent and prospective functioning in major depressive disorder. Emotion. 2, 135-146.

Rush, A.J., Thase, M.E., Dubé, S., 2003. Research issues in the study of difficult-to-treat depression. Biol Psychiatry.53, 743-753.

Serra, M., Salgado-Pineda, P., Delaveau, P., Fakra, E., Gasto, C., Blin, O., 2006. Effects of antidepressant drugs on emotion. Clin Neuropharmacol.29,170-185.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Fakra, E., Gasto, C., Blin, O., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 59, 22-33.

Steele, J.D., Christmas, D., Eljamel, M.S., Matthews, K., 2008. Anterior cingulotomy for major depression: clinical outcome and relationship to lesion characteristics. Biol Psychiatry.63,670-677.

Sullivan, R.M., Gratton, A., 1999. Lateralized effects of medial prefrontal cortex lesions on neuroendocrine and autonomic stress responses in rats. J Neurosci.19,2834-2840.

Surguladze, S., Brammer, M.J., Keedwell, P., Giampietro, V., Young, A.W., Travis, M.J., Williams, S.C., Phillips, M.L., 2005. A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry. 57,201-209.

Wager, T.D., Phan, K.L., Liberzon, I., Taylor, S.F., 2003. Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. Neuroimage. 19, 513-531.

Zobel, A., Joe, A., Freymann, N., Clusmann, H., Schramm, J., Reinhardt, M., Biersack, H.J., Maier, W., Broich, K., 2005. Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach. Psychiatry Res.139,165-179.

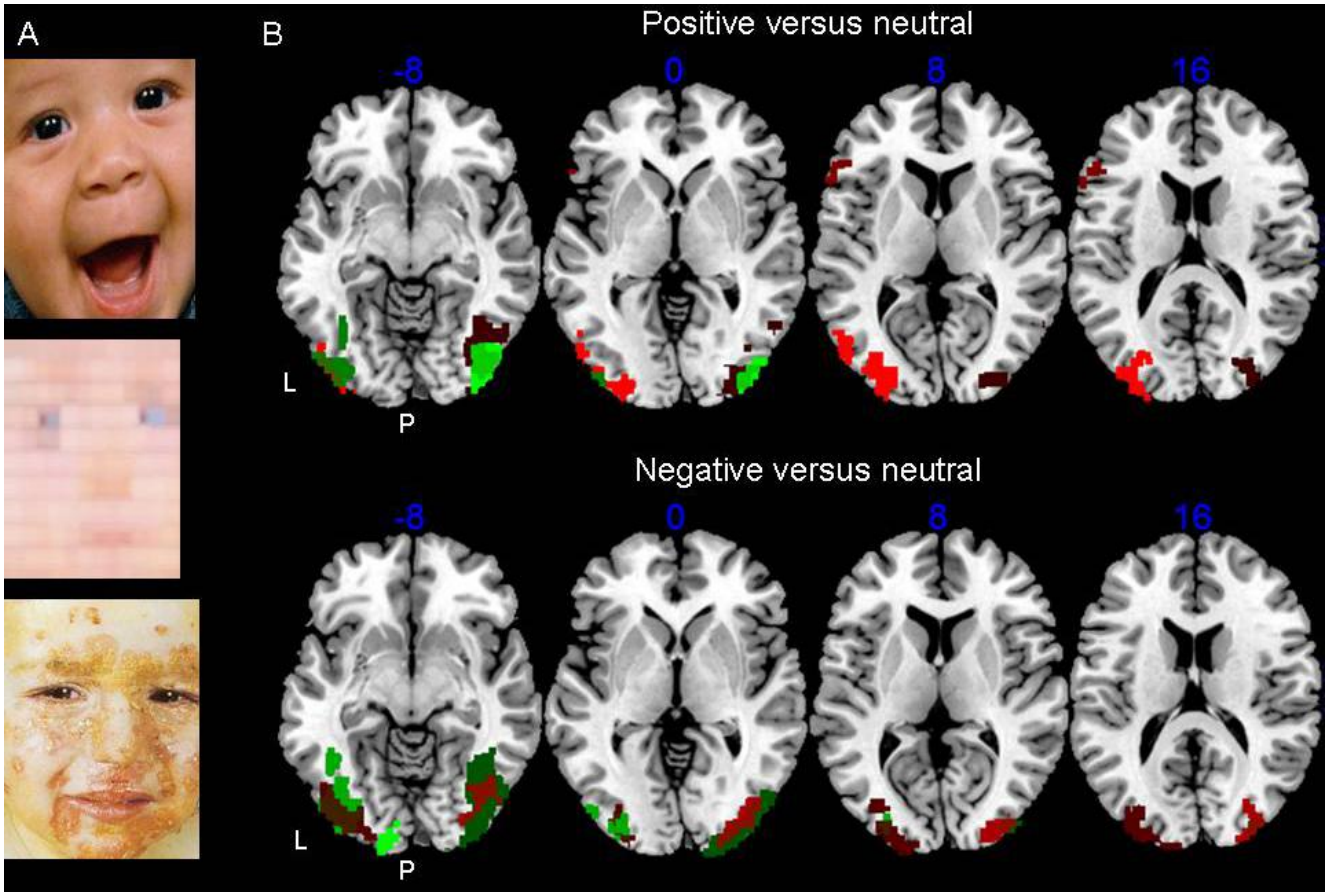

Fig 1.

A) Example of a 'positive', a 'neutral' and a 'negative' baby face.

B) Axial view of whole brain activity found in the random effects analysis (T-contrast, $p<0.001$, uncorrected) for the group of healthy women and melancholically depressed females overlaid on an anatomical T1-image for upper) the positive>neutral contrast and lower) the negative>neutral contrast. (L=left; P=posterior). The green areas represent the significantly activated clusters for the healthy subjects (largest cluster size for the positive>neutral contrast: 903; right inferior occipital gyrus (x=44, y=-80, z=-10) and largest cluster size for the negative>neutral contrast: 2256; right fusiform gyrus (x=36, y=-58, z=-10)). The red areas represent the significantly activated clusters for the

depressed patients (largest cluster size for the positive>neutral contrast: 2410; right inferior occipital gyrus (x=32, y=-92, z=-4) and largest cluster size for the negative>neutral contrast: 1596; right inferior occipital gyrus (x=34, y=-84, z=-4)). Brown colors represent overlap of neuronal activity between the two groups.

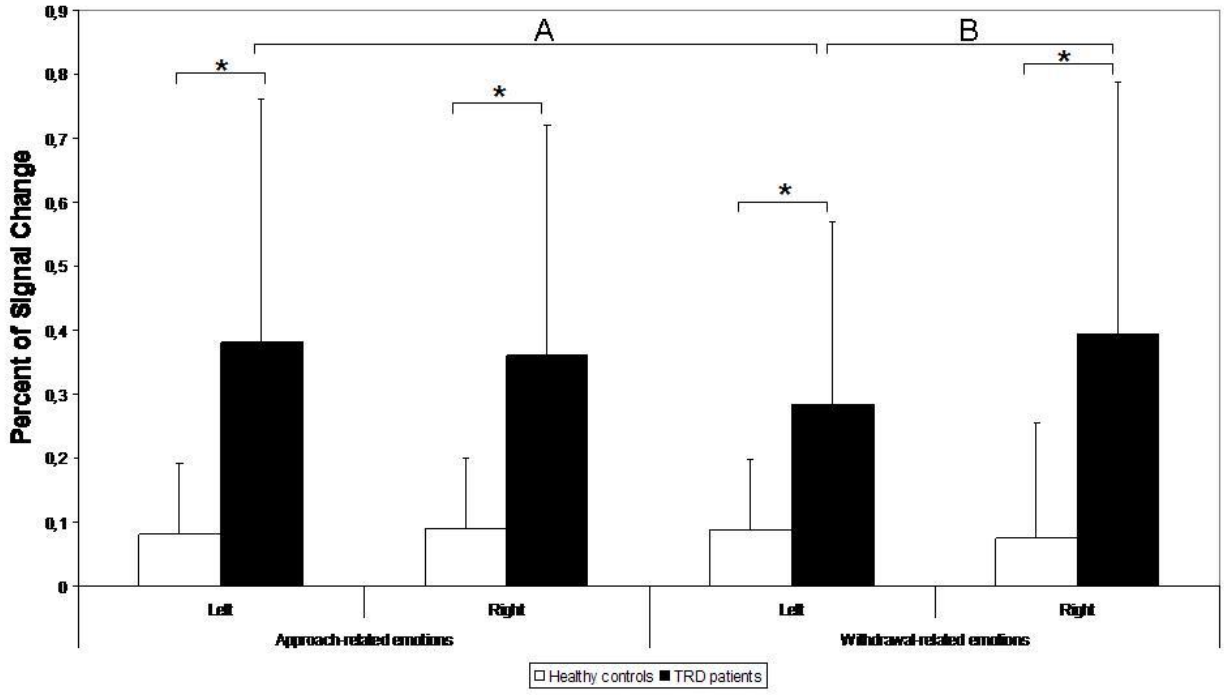

Fig 2:

Bar graph representing mean effects sizes and standard deviations of the approach- and withdrawal-related emotional experiences for the left and right subgenual prefrontal cortex in healthy controls and TRD patients (Cg25: Brodmann area 25). TRD= treatment-resistant depressed patients. (*) significant differences between healthy controls and TRD patients at $p \leq 0.05$.

A: Significantly lower left Cg25 activity in the withdrawal-related emotional experience compared to the approach-related emotional experience in TRD patients. B: Significantly lower left-sided Cg25 activity in the withdrawal-related emotional experience compared to the right in TRD patients. Significance threshold was set at a two-tailed probability of $p \leq 0.05$ for all analyses.

Voxel height threshold at P<0.001 significance uncorrected for multiple comparisons						
Cluster size	**Activation pattern**	**Anatomical region**	**Hemisphere**	**BA**	**Peak T value**	**Peak coordinates (x,y,z) (mm)**
T-contrast positive versus neutral						
Patients						
2410	P>n	Inferior occipital gyrus	Right	18	11.27	32 -92 -4
1312	P>n	Precuneus	Left	19	10.03	-22 -74 34
209	P>n	Inferior Frontal Gyrus	Left	45	4.29	-60 20 10
Controls						
903	P>n	Inferior occipital gyrus	Right	18	23.97	44 -80 -10
671	P>n	Inferior occipital gyrus	Left	18	4.38	-34 -82 -12
T-contrast negative versus neutral						
Patients						
1596	N>n	Inferior occipital gyrus	Right	18	7.99	34 -84 -4
1324	N>n	Middle Occipital Gyrus	Left	19	8.22	-34 -92 16
291	N>n	Fusiform gyrus	Left	37	7.02	-44 -64 -30
Controls						
2256	N>n	Fusiform gyrus	Right	37	21.65	36 -58 -10
1460	N>n	Fusiform gyrus	Left	37	9.72	-42 -54 -6
109	N>n	Lingual Gyrus	Left	17	5.65	-12 -96 -6

Table 1: Results of the random effects analysis for the contrasts positive versus neutral, negative versus neutral for all female subjects. We listed only those clusters with a significance of p(uncorrected)<0.001 and a cluster size>100. For each cluster, we reported the T-value and MNI coordinates at the position of the maximum, the cluster size and the appropriate Brodmann area (BA). P:positive. N:negative. n:neutral.